IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yan, et al.

Art Unit: 1632

Serial No.: 10/032,495

Examiner: Qian, Janice Li

Filed: January 2, 2002

Atty. Docket: 967039.00002

For: A Method For Producing A Population of Homozygous Stem Cells Having a Pre-Selected Immunotype And/Or Genotype, Cells Suitable For Transplant Derived Therefrom, And Materials And Methods Using Same

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned Steve Chien-Wen Huang, a citizen of Taiwan, residing at 19922 Dunstable Circle, Germantown, MD 20876, hereby declare and state that:

1. I am an inventor of the subject matter disclosed and claimed in the above-captioned application (hereinafter, "the application), and I performed and/or supervised work described in the application.

2. I was employed by Stemron, Inc. from October 1, 2001 to November 15, 2002. During that time, I conducted research and development relating to the methods claimed in the application and have further conducted research and development relating to (1) parthenogenetic activation of oocytes and generating pluripotent stem cells from said activated oocytes; (2) producing mouse homozygous stem cells having pre-selected immunotype and/or genotype; (3) evaluation of the derived mouse stem cells for their suitability for transplant; and (4) in vitro differentiation of the derived mouse stem cells into different somatic lineages.

3. I have read the Office Action mailed on November 2, 2004 concerning the above-captioned application. I understand that the Examiner has rejected Claims 29, 31 and 32 under 35 U.S.C. §§ 101 and 112, 1st paragraph, as failing to support the assertion that human homozygous pluripotent stem cells are obtainable by the claimed method so that a practical utility can be well established. Further, the Examiner asserts that the only utility for establishing a cell depository is to carry out further research to characterize the stem cells, which is not considered specific and substantial. The Examiner also rejected Claims 29, and 31-33 under 35 U.S.C. §112, 1st paragraph, as failing to comply with the enablement requirement because the specification fails to provide evidence to the contrary of the cited art of record that human pluripotent stem cells cannot be created by the method in the instant specification.

4. The instant application was filed on January 2, 2002, and claims priority to U.S. application 60/258,881 filed on January 2, 2001.

5. The disclosed methods of creating human pluripotent stem cells that are homozygous are enabled by the specification.

6. As evidence of the disclosure being enabled, others have followed the work of the inventors and successfully created pluripotent stem cells following the methods disclosed in the instant specification, i.e., Cibelli, et al., Parthenogenetic Stem Cells in Nonhuman Primates, Science, Vol. 295, p. 819 (Feb. 2002) (Exhibit 1); and Vrana, et al., Nonhuman primate parthenogenetic stem cells, PNAS, Vol. 100, Suppl. 1, pp. 11911-11916 (Sept. 2003) (Exhibit 2).

7. The Cibelli, et al reference was published in February 2002.

8. The Vrana, et al. reference was published in September 2003.

9. The Vrana, et al. and Cibelli, et al. references were published after the filing date of the application and the application's claim to priority.

10. The Vrana, et al. reference describes in vitro parthenogenetic development of monkey (Macaca fascicularis) eggs to the blastocyst stage, and their use to create a

pluripotent line of stem cells. Vrana, et al. at p. 11911. This reference also refers to the Cibelli, et al. reference, in which the same authors reported the creation of a line of nonhuman primate stem cells from parthenogenetically activated eggs. Science, Vol. 295, p. 819 (Feb. 2002)

11. The Vrana, et al. reference describes the creation of a pluripotent stem cell line (Cyno-1) using the same methods as disclosed in the application. "Mature metaphase II eggs were subsequently activated by incubation in 10 μM ionomycin for 8 min, followed by culture with 2 mM 6-dimethylaminopurine for 4 h. The inner cell masses (ICM) were isolated by immunosurgery as described (20) and cultured on a feeder layer of mitotically inactive mouse embryonic fibroblasts in Dulbecco's minimal essential medium (GIBCO) with 15% FCS (HyClone)." Vrana, et al. at p. 11912.

12. The Cibelli, et al. reference also references the article entitled, "Parthenogenetic Activation of Rhesus Monkey Oocytes and Reconstructed Embryos," Mitalipov, et al., Biol. Reprod., Vol. 65, pp. 253-259 (March 2001) (Exhibit 3), as the protocols used to parthenogenetically activate primate oocytes.

13. The Mitalipov, et al. reference was published in March of 2001, which is after the priority date of the instant application.

14. The Mitalipov, et al. reference describes the parthenogenetic activation of metaphase II oocytes by exposure to 5μM ionomycin for 2, 3, or 4 minutes, followed by incubation in 2mM 6-dimethylaminopurine (DMAP) for 4 hours. Mitalipov, et al. at p. 255. According to the authors of the reference this technique is one of the methods that they "identified [as] simple yet effective methods of oocyte activation in the monkey." Mitalipov, et al. at p. 258.

15. The instant application describes activation by exposing oocytes to agents such as Ca++ ionophore (ionomycin) followed by 6-dimethylaminopurine (6-DMAP). See Specification, p. 22, lines 7-12 and p. 44, lines 8-12. Specifically, in Example 1(c), human oocytes were exposed to 5 μM ionophore (ionomycin) for 5 minutes followed by incubation in 1-5 mM DMAP for 3 to 5 hours. Specification, p. 44, lines 8-12. The application also describes isolating the inner cell mass and culturing them on a feeder

cell layer with a medium consisting of Dulbecco's medium. See specification, p. 44, line 15 – p. 45, line 4.

16. Vrana, et al. and Cibelli, et al. following the methods disclosed in the application were able to create a pluripotent stem cell line using monkey oocytes.

17. As further evidence of the disclosure being enabling, the Hwang, et al. reference ("Evidence of a Pluripotent Human Embryonic Stem Cell Line from a Cloned Blastocyst," Science, Vol. 303(5664), pp. 1669-74 (Mar. 12, 2004; Epub. Feb. 12, 2004) also describes the parthenogenetic activation of human oocytes carrying somatic cell nuclei using the methods described in the instant application.

18. The Hwang, et al. reference was published in February 2004, which is after the filing and priority date of the instant application.

19. Specifically, the Hwang, et al. reference states, "[w]e found that incubation in 10 μM A23187 [calcium ionophore] for 5 min, followed by incubation with 2.0 mM 6-dimethylaminopurine (DAMP) for 4 hours, gave efficient chemical activation for human SCNT eggs." Hwang, et al., at p. 1670, column 3, lines 8-12. "A total of 30 SCNT-derived blastocysts were cultured, 20 ICMs were isolated by immunosurgical removal of the trophoblast, and one ES cell line (SCNT-hES-1) was derived." Hwang, et al. at p. 1670, column 3, lines 50-53.

20. The Hwang, et al. reference shows that, following the methods disclosed in the application, the authors were able to create a pluripotent stem cell line from parthenogenetically activated human SCNT (somatic cell nuclear transfer) oocytes.

21. The success of others using the methods disclosed in the application to make a pluripotent stem cell line, illustrates that the application is enabling to one of ordinary skill in the art and satisfies the requirements of 35 U.S.C. §112, 1st paragraph.

22. The application sets forth a substantial and specific utility. The methods provide homozygous stem cell lines, homozygous for MHC haplotypes and histocompatible with any individual carrying the components of such haplotypes for the purpose of having a

constant, reliable, comprehensive supply of cells for study, diagnosis, transplant, and/or treatment, i.e., cell replacement and/or gene therapy. Further, the homozygous stem cell lines are already characterized for MHC haplotypes. Therefore, further research is not required to characterize the homozygous stem cells. Thus, the application has a specific and substantial utility under 35 U.S.C. §101 and one of ordinary skill in the art would be able to operate the claimed invention as intended without undue experimentation thereby satisfying 35 U.S.C. §112, 1st paragraph.

23. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents ensuing thereon.

Respectfully submitted,

Steve Chien-Wen Huang

Date: 12-15-2004

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